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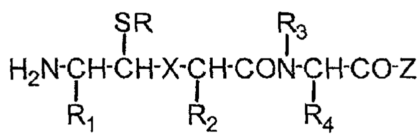
US CLAIMS

1. A compound of general formula I :



I

wherein :

• R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

– -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

– SO_3H group, optionally protected by a pentyl group,

– PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or

– tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted

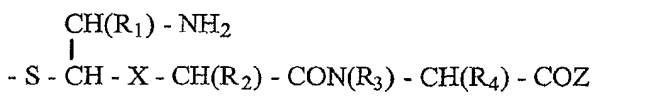
by at least one CO_2H group optionally protected, or

• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a group CONH or CH_2NH,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R"' wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

and the derivatives thereof.

2. The compound according to claim 1, wherein :

• R_4 denotes an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally being protected as described above, or

• R_4 constitutes with R_3 a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally being protected.

3. The compound according to claim 1, wherein R_4 and R_3 together constitute a 5- or 6-membered, heterocyclic compound substituted by at least one group CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 with the groups CO_2H, SO_3H and PO_3H_2 optionally being protected.

4. The compound according to claim 1, wherein X denotes a CONH function.

5. The compound according to claim 1, wherein R_2 denotes an optionally substituted alkyl or arylalkyl chain.

6.The compound according to claim 1, which is selected from the group consisting in :

N-[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Tyr-L.Sal-OH ;

N-[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Tyr-L.hSal-OH ;

N-[[(2S,3R)- and (2R,3R)-3-amino-5-carboxy-2-mercapto] pentanoyl]-L.Ile-L.(3R)(3-COOH)Pro-OH ;

N-[[(2S,3R)- and (2R,3R)-3-amino-5-phosphonate-2-mercapto] pentanoyl]-L.Ile-L.Glu-OH ;

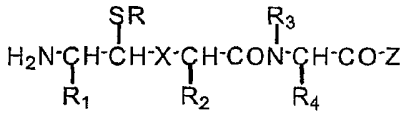
the N-[[2S,3R) and (2R,3R), 3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.Sal-OH ;

N-[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.(3R)(3-COOH)Pro-OH ;

N-[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.(3S)(3-COOH)Pro-OH ; and

N-[[(2S,3R)- and (2R,3R)-3-amino-2-mercapto-5-sulphonate] pentanoyl]-L.Ile-L.Glu-NH_2.

7. A process for preparing a compound of general formula I



I

wherein

• R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

– -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

– SO_3H group, optionally protected by a pentyl group,

– PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or

– tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

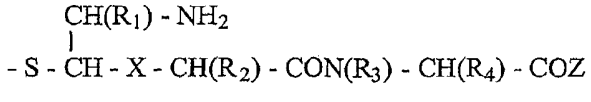
• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or

PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a group CONH,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R"' wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

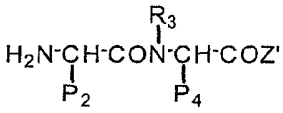
• R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

which involves at least coupling an ester dipeptide of general formula III



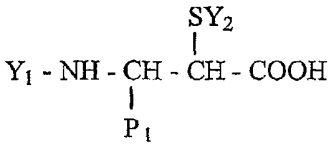
III

wherein

– P_2 and P_4 correspond to protected forms of R_2 and R_4,

– Z' denotes an $OC(CH_3)_3$, OCH_2-C_6H_5 or NR"R"' group wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, while R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N,

with a compound of general formula IV

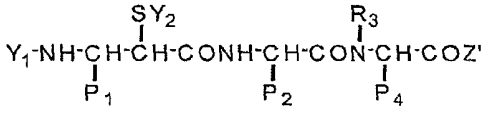


IV

wherein :

- Y_1 denotes a protecting group
- Y_2 denotes a protecting group and
- P_1 denotes a protected form of R_1,

under conditions suitable to produce compound V



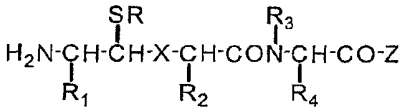
V

and deprotecting it for obtaining said compound of general formula I.

8. The process according to claim 7, wherein the coupling reaction is carried out in an organic solvent in the presence of a coupling agent and a tertiary amine and at a temperature of the order of 20°C.

9. A process according to claim 7, wherein the two asymmetric carbons of the dipeptide ester of general formula III have an S configuration.

10. A process for preparing a compound of general formula I



I

wherein :

- R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or

(cycloalkyl)alkyl group substituted by at least one

– -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

– SO_3H group, optionally protected by a pentyl group,

– PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or

– tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

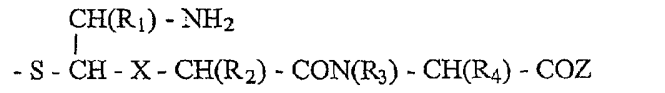
• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a CH_2-NH group,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R'" wherein R" and R'" independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R'" may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second

heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II

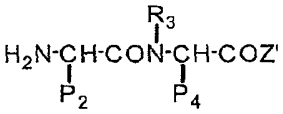


II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

which involves at least :

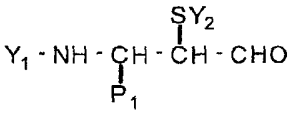
– condensing a compound of general formula III



III

wherein Z' denotes an $OC(CH_3)_3$, OCH_2-C_6H_5 or NR"R'" group with R" and R'" independently of one another may denoting a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R'" may, together with the nitrogen atom, constitute a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N,

with a compound of general formula VI,



VI

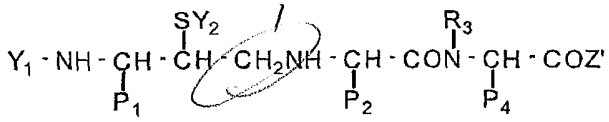
wherein :

– Y_1 denotes a protecting group

– Y_2 denotes a protecting group and

– P_1 denotes a protected form of R_1,

– reducing the intermediate thus formed to produce the compound of general formula VII

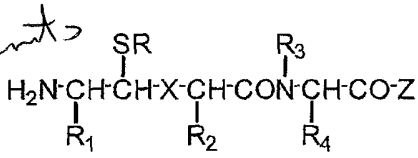


VII

by deprotecting the so-obtained compound and obtaining said compound of general formula I.

11. A process according to claim 9, wherein the two asymmetric carbons of the dipeptide ester of general formula III have an S configuration.

12. Use of a compound of formula (I) :



I

wherein :

• R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

– -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

– SO_3H group, optionally protected by a pentyl group,

– PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or

– tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

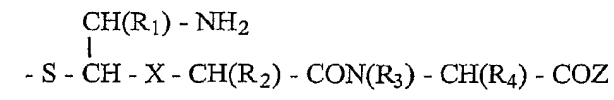
– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a group CONH or CH_2NH,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R"' wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

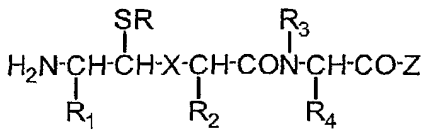
and the derivatives thereof,

as a selective inhibitor of aminopeptidase A.

13. Use according to claim 12 for preparing a medicament intended to reduce food intake, modulate anxiety states or panic attacks or treat essential

and secondary arterial hypertension, cardiac and renal failure, disorders of hydrodynamic homeostasis, myocardial infarct and proteinuria in diabetics.

14. Pharmaceutical composition containing as active ingredient at least one compound of general formula (I) :



I

wherein :

• R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

– -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

– SO_3H group, optionally protected by a pentyl group,

– PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or

– tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

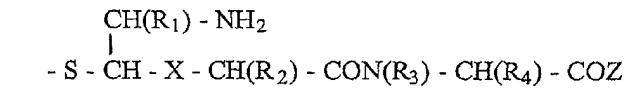
– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a group CONH or CH_2NH,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R"' wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II

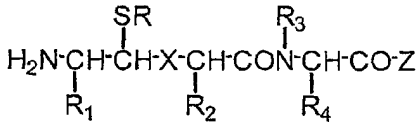


II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

and the derivatives thereof.

15. Diagnostic system for detecting and titrating aminopeptidase A, characterised in that it contains at least one compound of general formula (I):



I

wherein :

• R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

- -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,
- SO_3H group, optionally protected by a pentyl group,
- PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or
- tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

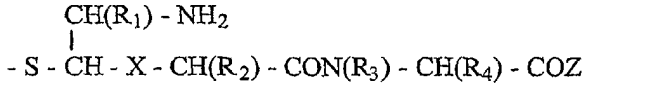
- an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,
- a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a group CONH or CH_2NH,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R"' wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II

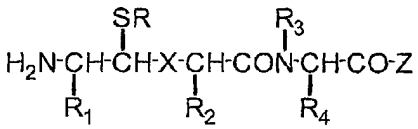


II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

and the derivatives thereof.

16. A method for the prevention or treatment of anxiety states or panic attacks, essential and secondary arterial hypertension, cardiac and renal failure, disorders of hydrodynamic homeostasis, myocardial infarct and proteinuria in diabetics, comprising administering to a patient in need of such treatment a therapeutically efficient amount of a compound of general formula (I) :



I

wherein :

• R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

– -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

– SO_3H group, optionally protected by a pentyl group,

– PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or

– tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

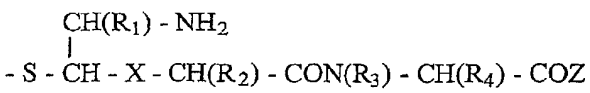
– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a group CONH or CH_2NH,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R"' wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II

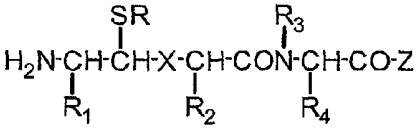


II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

and the derivatives thereof.

17. A method of diagnosis of anxiety states or panic attacks, essential and secondary arterial hypertension, cardiac and renal failure, disorders of hydrodynamic homeostasis, myocardial infarct and proteinuria in diabetics, wherein the aminopeptidase A is evaluated in a biological sample of a patient to be tested by using a compound of formula (I) :



I

wherein :

• R_1 denotes an alkyl, alkenyl or alkynyl chain, or a cycloalkyl or (cycloalkyl)alkyl group substituted by at least one

– -COOH group, optionally esterified by an alkyl group comprising 2 to 12 carbon atoms,

– SO_3H group, optionally protected by a pentyl group,

– PO_3H_2 group, optionally substituted by a ($-CH_2CH_2SCOR_5$) group, with R_5 representing a C_1-C_4 alkyl group, a phenyl or benzyl group, or

– tetrazolyl group.

• R_2 denotes an alkyl chain, or an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl group which may or may not be substituted by at least one OH, OR, SR', NH_2, NHR', guanidinyl, COOH or $CONH_2$ group, or a halogen atom selected from among F, Cl, Br or I with R' representing a straight-chain or branched C_{1-4} alkyl group.

• R_3 denotes a hydrogen atom or a methyl group,

• R_4 denotes

– an alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted

by at least one $CONH_2$, SO_3H, SO_2NH_2, PO_3H_2 or tetrazolyl group, with the groups SO_3H and PO_3H_2 optionally protected,

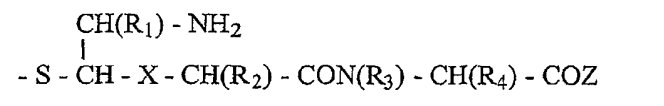
– a C_{2-6} alkyl chain, an aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, (heteroaryl)alkyl, heterocycloalkyl or (heterocycloalkyl)alkyl group substituted by at least one CO_2H group optionally protected, or

• R_3 and R_4 may together constitute a 5- or 6-membered heterocyclic compound, substituted by at least one CO_2H, $CONH_2$, SO_3H, SO_2NH_2 or PO_3H_2 group with the groups CO_2H, SO_3H and PO_3H_2 optionally protected,

• X denotes a group CONH or CH_2NH,

• Z denotes a group OH, OCH_2-C_6H_5 or NR"R"' wherein R" and R"' independently of one another may denote a hydrogen atom or an alkyl, aryl or arylalkyl group, where R" and R"' may constitute, together with the nitrogen atom, a 5- or 6-membered heterocycle possibly having a second heteroatom selected from among O, S and N, and

• R denotes a hydrogen atom or a group of formula II



II

corresponding to the symmetric disulphide of the inhibitor wherein R_1, R_2, R_3, R_4, X and Z are as hereinbefore defined,

and the derivatives thereof,

and is compared to the level present in normal subjects.